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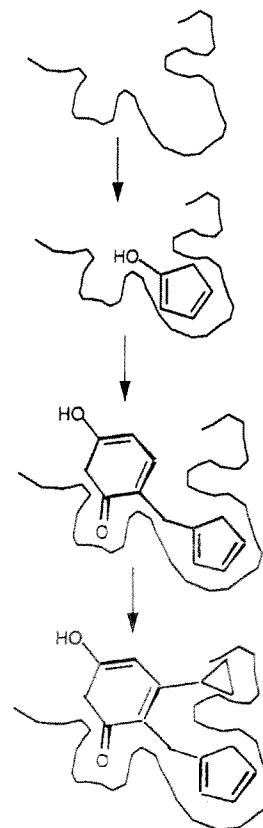
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : G01N 33/53, C30B 7/00</p>	<p>A3</p>	<p>(11) International Publication Number: WO 99/45379 (43) International Publication Date: 10 September 1999 (10.09.99)</p>
<p>(21) International Application Number: PCT/US99/04967 (22) International Filing Date: 5 March 1999 (05.03.99) (30) Priority Data: 09/036,184 6 March 1998 (06.03.98) US (71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors: NIENABER, Vicki, L.; 1136 Lamb Lane, Gurnee, IL 60031 (US). GREER, Jonathan; 6757 North Sacramento Avenue, Chicago, IL 60645 (US). ABAD-ZAPATERO, Celerino; 765 Greenview Place, Lake Forest, IL 60045 (US). NORBECK, Daniel, W.; 816 Walton Lane, Grayslake, IL 60030 (US). (74) Agents: STRODE, Janelle, D. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 25 November 1999 (25.11.99)</p>	

(54) Title: LIGAND SCREENING AND DESIGN BY X-RAY CRYSTALLOGRAPHY

(57) Abstract

X-ray crystallography can be used to screen compounds that are not known ligands of a target biomolecule for their ability to bind the target biomolecule. The method includes obtaining a crystal of a target biomolecule; exposing the target biomolecule crystal to one or more test samples; and obtaining an X-ray crystal diffraction pattern to determine whether a ligand/receptor complex is formed. The target is exposed to the test samples by either co-crystallizing a biomolecule in the presence of one or more test samples or soaking the biomolecule crystal in a solution of one or more test samples. In another embodiment, structural information from ligand/receptor complexes are used to design ligands that bind tighter, that bind more specifically, that have better biological activity or that have better safety profile. A further embodiment of the invention comprises identifying or designing biologically-active moieties by the instant process. In a further embodiment, a biomolecule crystal having an easily accessible active site is formed by co-crystallizing the biomolecule with a degradable ligand and degrading the ligand.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04967

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/53 C30B7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GREER, JONATHAN ET AL: "Application of the Three-Dimensional Structures of Protein Target Molecules in Structure-Based Drug Design" J. MED. CHEM. (1994), 37(8), 1035-54 , XP002116744	1-31, 33-35
X	cited in the application page 1046, column 1, paragraph 3 -page 1052, column 1, paragraph 3; figures 11,12 --- -/--	32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 September 1999

Date of mailing of the international search report

13/10/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04967

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NIENABER, VICKI L. ET AL: "A Noncleavable Retro-Binding Peptide That Spans the Substrate Binding Cleft of Serine Proteases. Atomic Structure of Nazumamide A: Human Thrombin" J. AM. CHEM. SOC. (1996), 118(29), 6807-6810, XP002116745 cited in the application	1-31, 33-35
X	page 6810, column 2 ---	32
A	VERLINDE, C. ET AL.: "Structure-based drug design: progress, results and challenges" STRUCTURE, vol. 2, no. 7, 15 July 1994 (1994-07-15), pages 577-587, XP002117026 cited in the application	1-31, 33-35
X	the whole document ---	32
A	VERLINDE, C. ET AL.: "In search of new lead compounds for trypanosomiasis drug design: A protein structure-based linked-fragment approach" JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN, vol. 6, no. 1, February 1992 (1992-02), pages 131-147, XP002117027 cited in the application	1-31, 33-35
X	the whole document -----	32

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/04967

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-31
SCREENING FOR UNKNOWN LIGANDS BY X-RAY CRYSTALLOGRAPHY

2. Claims: 32-35
CO-CRYSTALLATION OF BIOMOLECULES WITH LIGANDS